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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,625	KUFER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *3,5,8-18,24,25 and 27-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,19-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group 8, encompassing claims 1-7, 19-23, and 26, with species election of four functional domains and a histidine tag, in the reply filed on 16 April 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-18, 24, 25, 27-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 3, and 5 are also withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-41 are pending. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are examined on merits.

The Office has considered the references cited in the International Search Report (ISR) for PCT/EP99/05416 filed on 07/28/1999.

Claim Objections

Claim 1 is objected because of the limitation "produceable" in line 1. Merriam-Webster Online Dictionary downloaded on 7/1/2004 from url>>www.m-w.com teaches that the adjective for "produce" is "producible". Appropriate correction is required.

Claims 4, 6, 7, 19-23, and 26 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the

alternative only and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). For a compact prosecution purpose, the multiply dependent claims are be examined and interpreted to the best of the Office's ability. However, this treatment does not relieve applicant the burden of responding to this objection.

Claim 19-23, and 26 are also objected because the claims depend on non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the functional domains" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 4 is rejected because it depends on the rejected base claim 2.

Claim 6, which depends on claim 1 among other claims, is confusing because of "said domains" in line 2. Claim 6 appears to further limit what kind(s) of (poly)peptides are attached to either CH1 or CL1 of the base claim 1. The limitation "domains" in base claim 1 is used in context of either CH1, or CL domains, not the (poly)peptides having different receptor or ligand function.

Claim 7, which depends on claim 1 among other claims, is confusing because of "said domains" in line 2. Claim 7 appears to further limit what kind(s) of (poly)peptides

are attached to either CH1 or CL1 of the base claim 1. The limitation "domains" in base claim 1 is used in context of either CH1, or CL domains, not the (poly)peptides having different receptor or ligand function.

Claim 19 recites the limitation "said constant domain" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites the limitation "said constant immunoglobulin domains" in lines 1-2, and also recites the limitation "said functional receptor-ligand domains" in lines 2-3. There is insufficient antecedent basis for these limitations in the claim. Claims 21-23 are rejected because they depend on the rejected base claim 20.

Claim 26 recites, "CH1 domain is **limited** to a histidine tag" but it is not clear what the metes and bounds are. The instant application for example, claim 1, uses the limitation "linked" to indicate a connection of various polypeptides, for example certain immunoglobulin domains to other useful peptides such as polypeptides that bind to a tumor associated antigen. Based on the disclosure at Fig. 1, the Office assumes that "limited" means "linked" for the purpose of the Office action. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Muller et al., (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) as evidenced by WO 97/01580 (a copy provided with ISR).

The claims are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the heterodimer is not formed by interaction between the two polypeptides but formed by CH1 domain and CL domain, wherein said two polypeptides bind different receptors or have different ligand functions (claim **1**), wherein claim **2** describes how the two polypeptides are linked to either said CH1 domain or said CL1 domain i.e., C-and/or-N-terminal, wherein claim **4** further limits said heterodimer to have four functional domains, wherein claim **6** further limits at least one of the two polypeptides to be a scFv-fragment, wherein claim **7** further limits at least one of the two polypeptides to have an antigen binding region specific for a tumor associated antigen, wherein claim **19** further limits said CL1 domain to be from kappa chain of an immunoglobulin, wherein claims 20-22 further limit how said CH1 domain or said CL domain is connected to the different polypeptides, namely by a polypeptide linker (claim **20**), an Ig-hinge region (claim **21**), or an IgG hinge region (claim **22**), wherein claim **26** further limits said CH1 domain be linked to a histidine tag.

Muller et al., teach a heterodimer comprising two monomers, wherein the first monomer comprises CH1 domain linked via C-and/or-N-terminal to two functional

domains i.e. VH and VL functional domains of anti-EGF-R scFv fragment, and the second monomer comprises CL1 linked via C-and/or-N-terminal to two other functional domains i.e. VH and VL functional domains of anti-CD2 scFv fragment (total four functional domains in the multifunctional compound, as specified instant claim 4), wherein the two different polypeptides (i.e. anti-EGF-R scFv fragment and anti-CD2 scFv fragment) lack an intrinsic affinity for one another, wherein the heterodimer is formed by a disulfide bond between the CH1 domain of the first monomer and the CL domain of the second monomer (note Fig.1, the heading "Materials and methods" at pages 259-261, and Fig. 2), wherein at least one of the two monomers is to be able to bind a tumor associated antigen (note page 259, right column, 1st paragraph, where it teaches "miniantibodies capable of binding to the EGR receptor" that is "overexpressed by a wide range of tumors"), wherein said CL1 domain is from the kappa type chain of an immunoglobulin (note line 8 under the sub-heading "plasmid construction" at page 259, left column), wherein the CH1 domain or the CL domain is connected to the different four functional domains, at least two of the four functional domains having a ligand function to a EGF receptor (note page 259, 1st paragraph), namely by a polypeptide linker, or an Ig-hinge region, more specifically an IgG hinge region (note line 8 under the sub-heading "plasmid construction" at page 259, left column and Fig. 1B), wherein the CH1 domain is linked to a histidine tag (note line 2 from bottom of page 259, left column under the sub-heading "plasmid construction" and Fig. 1B).

The recitation of "produceable in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains" in claim 1 does not appear to limit

either the function and/or structure of the claimed multifunctional compound. In other words, the instant claim 1 appears to say that the claimed multifunctional compound **can be** produced "in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains". WO 97/01580 is cite to demonstrate that a multifunctional compound can be produced in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains before the effective filing date of the instant application. 97/01580 at page 16 especially lines 16 "a mammalian" host cell can be use to produce an engineered fully functional heterodimer antibody, and also teach at page 18 especially lines 4-20 a secretion signal that could be used in a mammalian expression system. Thus, the claimed multifunctional compound could be producible in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains. The Office emphasizes that WO 97/01580 is not cited to explain the structural limitation of the claimed multifunctional compound.

If the limitation "produceable in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains" in claim 1 is intended to specify how the claimed product is made, then the reference does not describe the production of the heterodimer using the method identical to that is recited in claim 1. However, the recitation of a process limitation in claim 1 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 1 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to

establish a patentable distinction between the claimed product and the product of the reference.

The method in which the heterodimer is produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process in a claim is the same from the product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., (30 January 1998, a copy provided with

ISR, FEBS Letters, vol. 422, pages 259-264) in view of Pluckthun and Pack (1997, Immunotechnology, vol. 3, pages 83-105).

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the linking is done by the **upper hinge region of human IgG3** (claim **23**). See the interpretation of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 above for further details.

As stated above in the rejection of 102(b), Muller et al., teach a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide with all the structural limitations of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26. See 102 (b) rejection above for further details. Muller et al., at the last sentence under the heading "Introduction" also teach why one of ordinary skill would be motivated to use a human sequence i.e. to reduce immunogenicity in a human subject.

Muller et al., do not specifically teach "the upper hinge region of human IgG3".

However, Pluckthun and Pack teach at page 89, left column, 1st paragraph "the use of hinge regions creates a spacing, hinge bending and rotational freedom of the associated scFv fragments, similar to the Fv-arms of a complete antibody...but with a fraction of its molecular weight. This was achieved by not adding the dimerization handle directly to the scFv fragment, but rather separated **by the upper hinge** from murine or **human Ig3**, known to lead to a flexible arrangements of domains". Further,

Pluckthun and Pack teach at the paragraph bridging pages 95-96 that a human IgG hinge region has been used for therapeutic application, which requires reduced "immunogenicity" in a human clinical application.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute the linkers of Muller et al., with the upper hinge region of human IgG3 taught by Pluckthun and Pack, to make a multifunctional compound. This would have been accomplished with a reasonable expectation of success since combination of Muller et al., (Jan. 1998) and Pluckthun and Pack (1997) teach how to make each elements of the claimed invention. One of ordinary skill in the art would have been motivated to make and use the claimed multifunctional compound using the upper hinge region of human IgG3 as the linker because Pluckthun and Pack teach that the upper hinge region of human IgG3 is good for reducing immunogenicity in a human patient and the human IgG3 is also good for its flexibility.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

Misook Yu